Search Strategy

FILE 'MEDLINE' ENTERED AT 01:16:17 ON 23 JUN 2003

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                E VEAS F/AU
L1           19 S E3 OR E4
                E CERUTTI M/AU
L2           65 S E3 OR E8
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FILE 'USPATFULL' ENTERED AT 01:17:37 ON 23 JUN 2003

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                E VEAS FRANCISCO/IN
L3            2 S E3
                E CERUTTI MARTINE/IN
L4            7 S E3
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FILE 'MEDLINE' ENTERED AT 01:18:30 ON 23 JUN 2003

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L5       131782 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L6        12160 S L5 AND (ENV? OR GP120 OR GP160)
L7         1343 S L6 AND (MUTANT? OR MUTEIN? OR VARIANT?)
L8           39 S L7 AND (ALPHA-HELIC? OR ALPHA-HELIX OR C1)
L9           34 S L7 AND (CONSTANT OR C1)
L10          21 S L9 NOT L8
                E HAIGWOOD N/AU
L11          47 S E3-E5
L12           2 S L11 AND (MUTANT? OR MUTEIN?)
L13          15 S L7 AND (112 OR 427 OR 479 OR 338)
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FILE 'MEDLINE' ENTERED AT 19:00:31 ON 23 JUN 2003

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                E THALI M/AU
L1           38 S E3 OR E4
L2            6 S L1 AND PY=1992
                E KWONG P D/AU
L3           21 S E3
L4            4 S L3 AND PY=1998
                E MISSE D/AU
L5            6 S E3 OR E4
                E CORDONNIER A/AU
L6           18 S E3-E6
L7            3 S L6 AND PY=1989
L8           15 S L6 NOT L7
                E HANSEN J E/AU
L9          204 S E3 OR E4
L10          11 S L9 AND PY=1996
L11      131782 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L12       12160 S L11 AND (ENV? OR GP120 OR GP160)
L13          99 S L12 AND (112 OR 427 OR 479 OR 338 OR W427G OR W479S OR W112G
L14         865 S L12 AND (AMINO ACID CHANGES OR SUBSTITUT? OR REPLACE?)
L15           9 S L14 AND (CD4-BINDING REGION OR CD4-RECEPTOR BINDING OR BIND C
L16         192 S L14 AND (FUSION OR NON-INFECTIOUS OR REDUCED VIRULENCE)
L17         189 S L16 NOT L15
L18          11 S L17 AND (C1 OR C4 OR C5 OR CONSERVED REGION)
L19           8 S L14 AND (FUSION INHIBITION OR INHIBIT? FUSION OR DECREASED IN
L20          26 S L14 AND (SEQUENCE VARIATION OR GENOTYPIC VARIATION OR GENETIC
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     FILE 'USPATFULL' ENTERED AT 20:09:44 ON 23 JUN 2003

L21       24988 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L22       15853 S L21 AND (GP120 OR GP160 OR ENV?)
L23        8443 S L22 AND (112 OR 427 OR 479 OR 338 OR W427G OR W479S OR W112G
L24        7811 S L23 AND (AMINO ACID CHANGES OR SUBSTITUT? OR REPLACE?)
L25         377 S L24 AND (CD4-BINDING OR CD4-RECEPTOR OR BINDING CD4 ANTIGEN)
L26         370 S L25 AND (INFECTION OR FUSION OR ENTRY)
L27         203 S L26 AND (C1 OR C4 OR C5 OR V3 OR CONSERVED REGION?)

     FILE 'WPIDS' ENTERED AT 20:14:23 ON 23 JUN 2003

               E VEAS F/IN
L28           6 S E3
L29       15446 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L30        1354 S L29 AND (GP120 OR GP160 OR ENV?)
L31         128 S L30 AND (AMINO ACID CHANGES OR SUBSTITUT? OR REPLACEMENT)
L32          72 S L31 AND (CD4-BINDING OR RECEPTOR BINDING OR BINDING CD4 ANTIG
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L1 ANSWER 6 OF 19 MEDLINE
1998362132 Document Number: 98362132. PubMed ID: 9696823. Dissociation of the CD4 and CXCR4 binding properties of human immunodeficiency virus type 1 gp120 by deletion of the first putative alpha-helical conserved structure. Misse D; Cerutti M; Schmidt I; Jansen A; Devauchelle G; Jansen F; Veas F. (Laboratoire d'Immunologie Retrovirale, Institut Francais de Recherches pour le Developpement en Cooperation, 34032 Montpellier, France.) JOURNAL OF VIROLOGY, (1998 Sep) 72 (9) 7280-8. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB To evaluate conserved structures of the surface gp120 subunit (SU) of the human immunodeficiency virus type 1 (HIV-1) envelope in gp120-cell interactions, we designed and produced an HIV-1 IIIB (HXB2R) gp120 carrying a deletion of amino acids E61 to S85. This sequence corresponds to a highly conserved predicted amphipathic alpha-helical structure located in the gp120 C1 region. The resultant soluble mutant with a deleted alpha helix 1 (gp120 DeltaalphaHX1) exhibited a strong interaction with CXCR4, although CD4 binding was undetectable. The former interaction was specific since it inhibited the binding of the anti-CXCR4 monoclonal antibody (12G5), as well as SDF1alpha, the natural ligand of CXCR4. Additionally, the mutant gp120 was able to bind to CXCR4(+)/CD4(-) cells but not to CXCR4(-)/CD4(-) cells. Although efficiently expressed on cell surface, HIV envelope harboring the deleted gp120 DeltaalphaHX1 associated with wild-type transmembrane gp41 was unable to induce cell-to-cell fusion with HeLa CD4(+) cells. Nevertheless, the soluble gp120 DeltaalphaHX1 efficiently inhibited a single round of HIV-1 LAI infection in HeLa P4 cells, with a 50% inhibitory concentration of 100 nM. Our data demonstrate that interaction with the CXCR4 coreceptor was maintained in a SUgp120 HIV envelope lacking alphaHX1. Moreover, in the absence of CD4 binding, the interaction of gp120 DeltaalphaHX1 with CXCR4 was sufficient to inhibit HIV-1 infection.

L2 ANSWER 2 OF 2 USPATFULL
2002:192270 Glycoprotein mutants of retrovirus envelopes and their biological applications.
Veas, Francisco, Mauguio, FRANCE
Jansen, Franz, Assas, FRANCE
Misse, Dorothee, Montpellier, FRANCE
US 2002103344 A1 20020801
APPLICATION: US 2001-960653 A1 20010924 (9)
PRIORITY: FR 1998-4056 19980401
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention concerns retrovirus envelope glycoprotein mutants characterized in that they are glycoproteins capable of specifically binding with chemokine receptors and having an inhibiting activity with respect to a retroviral infection.

CLM What is claimed is:
1. Glycoprotein mutants of HIV-1 gp120 envelopes, characterized in that they are glycoproteins capable of interacting specifically with the chemokine receptors and have an inhibiting activity with respect to an HIV-1 infection independent from CD4.

2.Mutants according to claim 1, characterized in that the deleted region corresponds to an .alpha. helix structure, such as is present in the native glycoproteins of envelope.

3. Mutants according to claim 1 or 2, characterized in that the deleted region corresponds to the .alpha.-1 helix structure such as is present in the Cl region of the native gp120 of HIV-1.

4. Mutants according to claim 3, characterized in that the deleted region corresponds to the fragment of sequence E61 to S85, such as is present in the Cl region of the native gp120 of HIV-1.

5. Mutants according to any one of claims 1 to 4, characterized in that the glycoproteins are recombinant.

6. Antibodies, characterized in that they are directed against the mutants according to any one of claims 1 to 5.

7. Application of the mutants according to any one of claims 1 to 5 as prototype viral envelopes for the study of their immunogenic power.

8. Application of the mutants according to any one of claims 1 to 5 as competitors of anti-viral drugs or antibodies at the virus receptor.

L12 ANSWER 2 OF 2 MEDLINE
91250322 Document Number: 91250322. PubMed ID: 2040587. Antibody reactivity to deletion mutants of the HIV-1 SF2 envelope. Back N K; Haigwood N L; de Wolf F; de Jongh B M; Goudsmit J. (Department of Virology, Academic Medical Centre, Amsterdam, The Netherlands.) INTERVIROLOGY, (1991) 32 (3) 160-72. Journal code: 0364265. ISSN: 0300-5526. Pub. country: Switzerland. Language: English.

AB In human immunodeficiency virus type 1 (HIV-1) infected individuals, the antibody response to the external envelope (gp120) is associated with in vitro neutralization. To further characterize the anti-gp120 response, we examined the IgG reactivity of 75 HIV-1-seroconverted and 200 HIV-1-seropositive individuals to deletion mutants of gp120 in an enzyme immunoassay. We used yeast-derived, non-glycosylated recombinant HIV-1 SF2 gp120 equivalent and-variants deleted in variable regions. We observed two distinctive response patterns: IgG non-responders (SF2-V3-restricted responders) and IgG responders to conserved regions of gp120. This divergence in response pattern occurred soon after gag/env HIV-1 antibody seroconversion and persisted in time within an individual. In addition, the SF2-V3-restricted responders had a higher frequency of HIV-1 core antigen positivity and HIV-1 core antibody negativity than the non-restricted responders. These results suggest that specific and persistent host antibody response patterns to gp120 develop early in HIV-1 infection and that these patterns are associated with differences in HIV-1 expression.

L13 ANSWER 14 OF 15 MEDLINE
92118456 Document Number: 92118456. PubMed ID: 1768461. Alteration of HIV-1 infectivity and neutralization by a single amino acid replacement in the V3 loop domain. Ivanoff L A; Looney D J; McDanal C; Morris J F; Wong-Staal F; Langlois A J; Petteway S R Jr; Matthews T J. (Department of Antiinfectives, SmithKline Beecham Pharmaceuticals, King of Prussia, PA 19406-0939.) AIDS RESEARCH AND HUMAN RETROVIRUSES, (1991 Jul) 7 (7) 595-603. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB The V3 loop (residues 303-338) of the human immunodeficiency virus type 1 (HIV-1) gp120 envelope protein represents a principal neutralizing determinant for the virus. An HIV-1 proviral clone containing a mutation in the V3 loop was constructed in which the proline residue at position 313 was changed to an alanine (P313-A). This mutation alters the conserved GPGR sequence that is found in the V3 loop sequences of different HIV-1 isolates. The P313-A clone produced virus particles, which were infectious for a number of T-cell lines including MOLT-4, CEM, and SupT1, but demonstrated a relatively low infectivity on the AA5 B-cell line when compared with wild-type viruses, HTLV-IIIB, HXB2/10 (a chimeric molecular clone), and another mutant virus (Q290-T). V3 loop-specific neutralizing polyclonal sera and the 9284 monoclonal antibody, which recognizes the amino side of the V3 loop sequence, effectively blocked infectivity and syncytia formation of all viruses tested. In contrast, the 0.5 beta monoclonal antibody, which is biologically more potent than 9284 and recognizes a different V3 loop determinant, failed to neutralize the P313-A virus. These results suggest that the proline residue in the relatively conserved GPGR "turn" region of the V3 loop is crucial for recognition by the 0.5 beta antibody. The observed variation in sensitivity of the B-cell line to the P313-A virus may reflect the presence of cell-specific factors which could be important in establishing an HIV-1 infection.

L13 ANSWER 13 OF 15 MEDLINE
94107600 Document Number: 94107600. PubMed ID: 7506556. A potent, neutralizing human monoclonal antibody against a unique epitope overlapping the CD4-binding site of HIV-1 gp120 that is broadly conserved across North American and African virus isolates. Pinter A; Honnen W J; Racho M E; Tilley S A. (Public Health Research Institute, New York, New York 10016.) AIDS RESEARCH AND HUMAN RETROVIRUSES, (1993 Oct) 9 (10) 985-96. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB A human monoclonal antibody (HuMAb), 5145A, against HIV-1 gp120 was isolated from an asymptomatic, seropositive hemophiliac. The epitope of this HuMAb was destroyed by reduction of gp120 disulfide bonds, but not by removal of N-linked carbohydrates. This epitope overlaps the CD4-binding site of gp120, because binding of 5145A to gp120 is inhibited by soluble CD4 and by 1125H, a previously described HuMAb directed toward the CD4-binding site. However, the 5145A epitope differs from those of 1125H and other anti-CD4-binding site HuMAbs previously described, as documented by the viral strain specificity of 5145A and its reactivity with a panel of gp120 mutants. Specifically, 5145A reacted with 14 of 15 HIV -1 isolates tested, including 9 isolates from the Central African Republic, 6 of which were not recognized by 1125H. Partial epitope mapping of 5145A, using a series of gp120 mutants, demonstrated its lack of sensitivity to mutations in residues 257 and 427, contrasting with a marked sensitivity to mutations in residues 368 and 370. This pattern of reactivity distinguishes its epitope from that of any HuMAb against the CD4-binding site region described to date. In addition, 5145A exhibited potent and essentially equivalent neutralization of the MN, SF-2, IIIB, and RF strains and possessed significant neutralizing activity against three of three African strains tested. Finally, 5145A synergistically neutralized the MN and SF-2 strains of HIV-1 when combined with 4117C, a HuMAb against the V3 loop. The broad strain specificity and potent neutralizing activity of 5145A, together with its ability to synergize with an anti-V3 loop HuMAb in neutralizing HIV-1, indicate that 5145A has excellent potential as a passive immunotherapeutic agent against HIV-1.

L13 ANSWER 5 OF 15 MEDLINE
1999412344 Document Number: 99412344. PubMed ID: 10482579. trans-dominant interference with human immunodeficiency virus type 1 replication and transmission in CD4(+) cells by an envelope double mutant. Chen S S; Lee S F; Chuang C K; Raj V S. (Division of Infectious Diseases, Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan, Republic of China.. schen@ibms.sinica.edu.tw) . JOURNAL OF VIROLOGY, (1999 Oct) 73 (10) 8290-302. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB We previously reported that a human immunodeficiency virus type 1 (HIV-1) envelope (Env) mutant with the whole cytoplasmic domain deleted, denoted mutant TC, is able to dominantly interfere with wild-type (wt) virus infectivity. In the present study, the feasibility of developing a dominant negative mutant-based genetic anti-HIV strategy targeting the gp41 cytoplasmic domain was investigated. Mutants TC and 427,TC, a TC derivative with a Trp-to-Ser substitution introduced into residue 427 in the CD4-binding site, and a series of mutants with deletions in the cytoplasmic domain, effectively trans-dominantly interfered with wt Env -mediated viral infectivity, as demonstrated by an env

trans-complementation assay. The syncytium formation-defective 427, TC double mutant not only inhibited heterologous LAV and ELI Env-mediated viral infectivity but also interfered with syncytium formation and infectivity mediated by the Env proteins of the two primary isolates 92BR and 92US. Stable HeLa-CD4-LTR-beta-gal clones that harbored Tat-controlled expression cassettes encoding the control DeltaKS, which had a deletion in the env gene, wt, or mutant env gene were generated. Viral transmission mediated by laboratory-adapted T-cell-tropic HXB2 and NL4-3 viruses was greatly reduced in the TC and 427,TC transfectants compared to that observed in the control DeltaKS and wt transfectants. Viral replication caused by HXB2 and NL4-3 viruses and by macrophage-tropic ConB and ADA-GG viruses was delayed or reduced in human CD4(+) T cells transfected with the 427,TC env construct compared to that observed in cells transfected with the control DeltaKS or TC env construct. The lack of significant interference by TC mutant was due neither to the lack of TC env gene integration into host DNA nor to the lack of TC Env expression upon Tat induction. These results indicate that this 427,TC Env double mutant has a role in the development of trans-dominant mutant-based genetic anti-HIV strategies.

L2 ANSWER 3 OF 6 MEDLINE

92365162 Document Number: 92365162. PubMed ID: 1380099. Discontinuous, conserved neutralization epitopes overlapping the CD4-binding region of human immunodeficiency virus type 1 gp120 envelope glycoprotein. Thali M; Furman C; Ho D D; Robinson J; Tilley S; Pinter A; Sodroski J. (Division of Human Retrovirology, Dana-Farber Cancer Institute, Boston, Massachusetts.) JOURNAL OF VIROLOGY, (1992 Sep) 66 (9) 5635-41. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Monoclonal antibodies have been isolated from human immunodeficiency virus type 1 (HIV-1)-infected patients that recognize discontinuous epitopes on the gp120 envelope glycoprotein, that block gp120 interaction with the CD4 receptor, and that neutralize a variety of HIV-1 isolates. Using a panel of HIV-1 gp120 mutants, we identified amino acids important for precipitation of the gp120 glycoprotein by three different monoclonal antibodies with these properties. These amino acids are located within seven discontinuous, conserved regions of the gp120 glycoprotein, four of which overlap those regions previously shown to be important for CD4 recognition. The pattern of sensitivity to amino acid change in these seven regions differed for each antibody and also differed from that of the CD4 glycoprotein. These results indicate that the CD4 receptor and this group of broadly neutralizing antibodies recognize distinct but overlapping gp120 determinants.

L4 ANSWER 1 OF 4 MEDLINE

1998303386 Document Number: 98303386. PubMed ID: 9641684. The antigenic structure of the HIV gp120 envelope glycoprotein. Wyatt R; Kwong P D; Desjardins E; Sweet R W; Robinson J; Hendrickson W A; Sodroski J G. (Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115, USA.) NATURE, (1998 Jun 18) 393 (6686) 705-11. Journal code: 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The human immunodeficiency virus HIV-1 establishes persistent infections in humans which lead to acquired immunodeficiency syndrome (AIDS). The HIV-1 envelope glycoproteins, gp120 and gp41, are assembled into a trimeric complex that mediates virus entry into target cells. HIV-1 entry

depends on the sequential interaction of the gp120 exterior envelope glycoprotein with the receptors on the cell, CD4 and members of the chemokine receptor family. The gp120 glycoprotein, which can be shed from the envelope complex, elicits both virus-neutralizing and non-neutralizing antibodies during natural infection. Antibodies that lack neutralizing activity are often directed against the gp120 regions that are occluded on the assembled trimer and which are exposed only upon shedding. Neutralizing antibodies, by contrast, must access the functional envelope glycoprotein complex and typically recognize conserved or variable epitopes near the receptor-binding regions. Here we describe the spatial organization of conserved neutralization epitopes on gp120, using epitope maps in conjunction with the X-ray crystal structure of a ternary complex that includes a gp120 core, CD4 and a neutralizing antibody. A large fraction of the predicted accessible surface of gp120 in the trimer is composed of variable, heavily glycosylated core and loop structures that surround the receptor-binding regions. Understanding the structural basis for the ability of HIV-1 to evade the humoral immune response should assist in the design of a vaccine.

L4 ANSWER 2 OF 4 MEDLINE
1998303379 Document Number: 98303379. PubMed ID: 9641677. Structure of an HIV gp120 envelope glycoprotein in complex with the CD4 receptor and a neutralizing human antibody. Kwong P D; Wyatt R; Robinson J; Sweet R W; Sodroski J; Hendrickson W A. (Department of Biochemistry and Molecular Biophysics, Columbia University, New York, New York 10032, USA.) NATURE, (1998 Jun 18) 393 (6686) 648-59. Journal code: 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The entry of human immunodeficiency virus (HIV) into cells requires the sequential interaction of the viral exterior envelope glycoprotein, gp120, with the CD4 glycoprotein and a chemokine receptor on the cell surface. These interactions initiate a fusion of the viral and cellular membranes. Although gp120 can elicit virus-neutralizing antibodies, HIV eludes the immune system. We have solved the X-ray crystal structure at 2.5 A resolution of an HIV-1 gp120 core complexed with a two-domain fragment of human CD4 and an antigen-binding fragment of a neutralizing antibody that blocks chemokine-receptor binding. The structure reveals a cavity-laden CD4-gp120 interface, a conserved binding site for the chemokine receptor, evidence for a conformational change upon CD4 binding, the nature of a CD4-induced antibody epitope, and specific mechanisms for immune evasion. Our results provide a framework for understanding the complex biology of HIV entry into cells and should guide efforts to intervene.

L5 ANSWER 6 OF 6 MEDLINE
1998362132 Document Number: 98362132. PubMed ID: 9696823. Dissociation of the CD4 and CXCR4 binding properties of human immunodeficiency virus type 1 gp120 by deletion of the first putative alpha-helical conserved structure. Misse D; Cerutti M; Schmidt I; Jansen A; Devauchelle G; Jansen F; Veas F. (Laboratoire d'Immunologie Retrovirale, Institut Francais de Recherches pour le Developpement en Cooperation, 34032 Montpellier, France.) JOURNAL OF VIROLOGY, (1998 Sep) 72 (9) 7280-8. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB To evaluate conserved structures of the surface gp120 subunit (SU) of the human immunodeficiency virus type 1 (HIV-1) envelope in gp120-cell interactions, we designed and produced an HIV-1 IIIB (HXB2R) gp120 carrying a deletion of amino acids E61 to S85. This sequence corresponds to a highly conserved predicted amphipathic alpha-helical structure located in the gp120 C1 region. The resultant soluble mutant with a

deleted alpha helix 1 (gp120 DeltaalphaHX1) exhibited a strong interaction with CXCR4, although CD4 binding was undetectable. The former interaction was specific since it inhibited the binding of the anti-CXCR4 monoclonal antibody (12G5), as well as SDF1alpha, the natural ligand of CXCR4. Additionally, the mutant gp120 was able to bind to CXCR4(+)/CD4(-) cells but not to CXCR4(-)/CD4(-) cells. Although efficiently expressed on cell surface, HIV envelope harboring the deleted gp120 DeltaalphaHX1 associated with wild-type transmembrane gp41 was unable to induce cell-to-cell fusion with HeLa CD4(+) cells. Nevertheless, the soluble gp120 DeltaalphaHX1 efficiently inhibited a single round of HIV-1 LAI infection in HeLa P4 cells, with a 50% inhibitory concentration of 100 nM. Our data demonstrate that interaction with the CXCR4 coreceptor was maintained in a SUgp120 HIV envelope lacking alphaHX1. Moreover, in the absence of CD4 binding, the interaction of gp120 DeltaalphaHX1 with CXCR4 was sufficient to inhibit HIV-1 infection.

L7 ANSWER 3 OF 3 MEDLINE
89365145 Document Number: 89365145. PubMed ID: 2475780. Single amino-acid changes in HIV envelope affect viral tropism and receptor binding. Cordonnier A; Montagnier L; Emerman M. (Unite d'Oncologie Virale (CNRS UA 1157), Institut Pasteur, Paris, France.) NATURE, (1989 Aug 17) 340 (6234) 571-4. Journal code: 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Infection by the human immunodeficiency virus (HIV) is initiated by the binding of its extracellular envelope glycoprotein, gp120, to the CD4 antigen on target cells. To map the residues of the HIV-1 glycoprotein that are critical for binding and to analyse the effects of binding on viral infectivity, we created 15 mutations in a region of gp120 that is important for binding to CD4 (refs 4,5). We find that substitution of a single amino acid (tryptophan at position 432) can abrogate CD4 binding and that virus carrying this mutation is non-infectious. By contrast, other amino-acid changes in the same region do not affect CD4 binding but restrict viral tropism: virions containing isoleucine substitutions at position 425 lose their ability to infect a monocyte cell line (U937 cells) but can still infect T-lymphocyte cell lines (CEM, SUP-T1) and activated human peripheral blood lymphocytes. These results indicate that cellular tropism of HIV can be influenced by a single amino-acid change in gp120.

L10 ANSWER 6 OF 11 MEDLINE
96323954 Document Number: 96323954. PubMed ID: 8727315. Prediction of the secondary structure of HIV-1 gp120. Hansen J E; Lund O; Nielsen J O; Brunak S; Hansen J E. (Laboratory for Infectious Diseases, Hvidovre Hospital, University of Copenhagen, Denmark.) PROTEINS, (1996 May) 25 (1) 1-11. Journal code: 8700181. ISSN: 0887-3585. Pub. country: United States. Language: English.

AB The secondary structure of HIV-1 gp120 was predicted using multiple alignment and a combination of two independent methods based on neural network and nearest-neighbor algorithms. The methods agreed on the secondary structure for 80% of the residues in BH10 gp120. Six helices were predicted in HIV strain BH10 gp120, as well as in 27 other HIV-1 strains examined. Two helical segments were predicted in regions displaying profound sequence variation, one in a region suggested to be critical for CD4 binding. The predicted content of helix, beta-strand, and coil was consistent with estimates from Fourier transform infrared spectroscopy. The predicted secondary structure of gp120 compared well with data from NMR analysis of synthetic peptides from the V3 loop and the C4 region. As a first step towards modeling the tertiary structure of gp120, the predicted secondary structure may guide the design of future

HIV subunit vaccine candidates.

L13 ANSWER 94 OF 99 MEDLINE
90155235 Document Number: 90155235. PubMed ID: 1689372. B cell epitope mapping of human immunodeficiency virus envelope glycoproteins with long (19- to 36-residue) synthetic peptides. Neurath A R; Strick N; Lee E S. (Lindsley F. Kimball Research Institute, New York Blood Center, New York 10021.) JOURNAL OF GENERAL VIROLOGY, (1990 Jan) 71 (Pt 1) 85-95. Journal code: 0077340. ISSN: 0022-1317. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Envelope glycoproteins, gp 120 and gp41, of the human immunodeficiency virus type 1 (HIV-1) elicit immune responses, including virus-neutralizing antibodies, which are expected to play a role in the defence against HIV-1 infection. Subregions of the gp120/gp41 sequence have immunosuppressive effects or may be implicated in autoimmune responses. Some of the immunodominant epitopes of gp120/gp41 do not contribute to protective immunity and act as immunological decoys. These circumstances emphasize the need to select from gp120/gp41 regions inducing protective responses. Towards this goal, 30 peptides covering approximately 87% of the HIV-1 strain BH10 gp120/gp41 sequence were synthesized. Antibodies in rabbit and human anti-HIV-1 sera recognized 28 and nine of the peptides, respectively, indicating that most of the gp120/gp41 sequence is immunogenic and secondly, that the antibody response to HIV-1 is restricted in infected humans. Most of the peptides, without conjugation to carriers, elicited high levels of anti-peptide (endpoints 1: greater than 10(4] and anti-gp120/gp41 (endpoints 1: greater than or equal to 10(3] antibodies. The highest levels of virus-neutralizing antibodies were elicited by peptide 306 to 338 from a hypervariable loop of gp120. Additional peptides from the full-length hypervariable loop (303 to 338) of HIV-1 BH10 and from 20 additional HIV-1 isolates were recognized differentially by human anti-HIV, suggesting that success of passive immunization may depend on a match between administered antibodies and the challenging HIV -1 strain, and also that active immunization with selected peptides from a hypervariable region of distinct HIV-1 isolates should be explored further as a method for prophylaxis against infection.

L13 ANSWER 90 OF 99 MEDLINE
91056537 Document Number: 91056537. PubMed ID: 2243375. Identification of individual human immunodeficiency virus type 1 gp120 amino acids important for CD4 receptor binding. Olshevsky U; Helseth E; Furman C; Li J; Haseltine W; Sodroski J. (Dana-Farber Cancer Institute, Department of Pathology, Harvard Medical School, Boston, Massachusetts.) JOURNAL OF VIROLOGY, (1990 Dec) 64 (12) 5701-7. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The binding of the CD4 receptor by the human immunodeficiency virus type 1 gp120 exterior envelope glycoprotein is important for virus entry and cytopathic effect. To investigate the CD4-binding region of the gp120 glycoprotein, we altered gp120 amino acids, excluding cysteines, that are conserved among the primate immunodeficiency viruses utilizing the CD4 receptor. Changes in two hydrophobic regions (Thr-257 in conserved region 2 and **Trp-427** in conserved region 4) and two hydrophilic regions (Asp-368 and Glu-370 in conserved region 3 and Asp-457 in conserved region 4) resulted in significant reductions in CD4 binding. For most of the mutations affecting these residues, the observed effects

on CD4 binding did not apparently result from global conformational disruption of the gp120 molecule, as assessed by measurements of precursor processing, subunit association, and monoclonal antibody recognition. The two hydrophilic regions exhibit a strong propensity for beta-turn formation, are predicted to act as efficient B-cell epitopes, and are located adjacent to hypervariable, glycosylated regions. This study defines a small number of gp120 residues important for CD4 binding, some of which might constitute attractive targets for immunologic intervention.

L13 ANSWER 69 OF 99 MEDLINE
93248254 Document Number: 93248254. PubMed ID: 8483933. Proposed atomic structure of a truncated human immunodeficiency virus glycoprotein gp120 derived by molecular modeling: target CD4 recognition and docking mechanism. Gabriel J L; Mitchell W M. (Department of Biochemistry, Temple University School of Medicine, Philadelphia, PA 19140.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1993 May 1) 90 (9) 4186-90. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The atomic structure of a truncated glycoprotein gp120 from human immunodeficiency virus 1 (HIV -1) that contains the principal neutralizing antigenic sites and the CD4 binding domain has been derived by molecular dynamics and calculation of potential energy using the DREIDING force field. The resultant N-glycosylated molecular model is consistent with known properties of gp120 and docks with CD4 with a substantial reduction in the sum of the internal potential energies of the individual proteins (delta E = -200 kcal/mol). The primary mechanism of recognition and binding is the insertion of the solvent-accessible Phe-43 of CD4 into a gp120 solvent-accessible acceptor pit formed by **Trp-427**, Tyr-435, and the high-mannose oligosaccharide N-linked to Asn-230. delta E for the nonglycosylated complex is reduced significantly (-75 kcal/mol). Binding is by pi-pi* interactions of the aromatic groups forming a hydrophobic, thermodynamically stable environment for these functional noncovalent bonding participants. This model for gp120 provides a theoretical basis for the evaluation of HIV molecular pathogenesis involving the env proteins, the analysis of conformation on functional immune response of the host, and the design of nonproteinaceous inhibitors specific for the CD4 binding site on gp120.

L15 ANSWER 9 OF 9 MEDLINE
90055841 Document Number: 90055841. PubMed ID: 2554859. A strategy simplifying site-directed mutagenesis in the CD4-binding region of HIV gp 120. Hemming A; Lundberg L; Olofsson S. (Department of Clinical Virology, University of Goteborg, Sweden.) ARCHIVES OF VIROLOGY, (1989) 107 (3-4) 301-5. Journal code: 7506870. ISSN: 0304-8608. Pub. country: Austria. Language: English.

AB By site-directed mutagenesis, two unique restriction sites, surrounding the CD4-binding DNA region of HIV gp 120, were created. The mutations do not cause amino acid substitutions but generate a DNA fragment, which is stable when cloned into M 13 for further mutagenesis and is also easy to reclone.

L15 ANSWER 8 OF 9 MEDLINE
90120974 Document Number: 90120974. PubMed ID: 2558637. Cystein 402 of HIV gp 120 is essential for CD4-binding and resistance of gp 120 to intracellular degradation. Hemming A; Bolmstedt A; Flodby P; Lundberg

L; Gidlund M; Wigzell H; Olofsson S. (Department of Clinical Virology, University of Goteborg, Sweden.) ARCHIVES OF VIROLOGY, (1989) 109 (3-4) 269-76. Journal code: 7506870. ISSN: 0304-8608. Pub. country: Austria. Language: English.

AB A DNA fragment encoding the CD4-binding region of human immunodeficiency virus type 1 (HIV) gp 120 was excised from an SV40-based expression vector containing gp 160, and subcloned into phage M13 for site-directed mutagenesis. Mutant vectors were constructed and CV-1 cells were transfected with constructs, where Cys402 was substituted for a serine, and metabolically labelled with [3H]-N-acetylglucosamine (GlcN). Radioimmunoprecipitation with an hyperimmunserum, specific for gp 120/gp 160, and subsequent SDS-polyacrylamide gel electrophoresis demonstrated presence of gp 160, whereas gp 120 was replaced by [3H]-GlcN-labelled material, migrating as a diffuse band corresponding to 80-105k, suggesting increased sensitivity of mutant env gene products to proteolysis after cleavage to gp 120. Wild type gp 120 and gp 160 bound to CD4, whereas neither gp 160 nor gp 120 from mutant-transfected cell lysates did bind to CD4. Altogether the results indicated that Cys402, probably by participating in a disulfide bridge, is essential for (i) the CD4-binding ability of env gene products and for (ii) the physical stability of gp 120.

L17 ANSWER 189 OF 189 MEDLINE
88062976 Document Number: 88062976. PubMed ID: 3257102. In vitro mutagenesis identifies a region within the envelope gene of the human immunodeficiency virus that is critical for infectivity. Willey R L; Smith D H; Lasky L A; Theodore T S; Earl P L; Moss B; Capon D J; Martin M A. (Laboratory of Molecular Microbiology, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland 20892.) JOURNAL OF VIROLOGY, (1988 Jan) 62 (1) 139-47. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Site-specific mutagenesis was used to introduce amino acid substitutions at the asparagine codons of four conserved potential N-linked glycosylation sites within the gp120 envelope protein of human immunodeficiency virus (HIV). One of these alterations resulted in the production of noninfectious virus particles. The amino acid substitution did not interfere with the synthesis, processing, and stability of the env gene polypeptides gp120 and gp41 or the binding of gp120 to its cellular receptor, the CD4 (T4) molecule. Vaccinia virus recombinants containing wild-type or mutant HIV env genes readily induced syncytia in CD4+ HeLa cells. These results suggest that alterations involving the second conserved domain of the HIV gp120 may interfere with an essential early step in the virus replication cycle other than binding to the CD4 receptor. In long-term cocultures of a T4+ lymphocyte cell line and colon carcinoma cells producing the mutant virus, revertant infectious virions were detected. Molecular characterization of two revertant proviral clones revealed the presence of the original mutation as well as a compensatory amino acid change in another region of HIV gp120.

L17 ANSWER 184 OF 189 MEDLINE
89342593 Document Number: 89342593. PubMed ID: 2547987. Functional interaction of constant and variable domains of human immunodeficiency virus type 1 gp120. Willey R L; Ross E K; Buckler-White A J; Theodore T S; Martin M A. (Laboratory of Molecular Microbiology, National Institute of Allergy and Infectious

Diseases, Bethesda, Maryland 20892.) JOURNAL OF VIROLOGY, (1989 Sep) 63 (9) 3595-600. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB A previously reported amino acid substitution within the second conserved domain of the human immunodeficiency virus type 1 (HIV-1) gp120 envelope results in the production of noninfectious particles. Molecular characterization of spontaneous revertant viruses, which arose during long-term cocultures of this env mutant, revealed that an amino acid change within another region of gp120 could functionally compensate for the mutation and restore infectivity. In the current study, we have introduced a conservative amino acid substitution at this second-site revertant codon and observed a marked reduction in HIV-1 infectivity. During the passage of this defective virus in cocultures, yet another revertant appeared which contained an amino acid change within a variable region of gp120 which restored infectivity to near wild-type levels. These results, in combination with other point mutations that have been introduced into the HIV-1 envelope, suggest that at least three discrete regions of gp120 may interact during the establishment of a productive viral infection. This critical step occurs subsequent to the adsorption of virions to the cell surface and either prior to or concomitant with the fusion of viral and cellular membranes.

L17 ANSWER 183 OF 189 MEDLINE
89365145 Document Number: 89365145. PubMed ID: 2475780. Single amino-acid changes in HIV envelope affect viral tropism and receptor binding. Cordonnier A; Montagnier L; Emerman M. (Unite d'Oncologie Virale (CNRS UA 1157), Institut Pasteur, Paris, France.) NATURE, (1989 Aug 17) 340 (6234) 571-4. Journal code: 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Infection by the human immunodeficiency virus (HIV) is initiated by the binding of its extracellular envelope glycoprotein, gp120, to the CD4 antigen on target cells. To map the residues of the HIV-1 glycoprotein that are critical for binding and to analyse the effects of binding on viral infectivity, we created 15 mutations in a region of gp120 that is important for binding to CD4 (refs 4,5). We find that substitution of a single amino acid (tryptophan at position 432) can abrogate CD4 binding and that virus carrying this mutation is non-infectious. By contrast, other amino-acid changes in the same region do not affect CD4 binding but restrict viral tropism: virions containing isoleucine substitutions at position 425 lose their ability to infect a monocyte cell line (U937 cells) but can still infect T-lymphocyte cell lines (CEM, SUP-T1) and activated human peripheral blood lymphocytes. These results indicate that cellular tropism of HIV can be influenced by a single amino-acid change in gp120.

L17 ANSWER 170 OF 189 MEDLINE
92085424 Document Number: 92085424. PubMed ID: 1727497. Analysis of mutations in the V3 domain of gp160 that affect fusion and infectivity. Page K A; Stearns S M; Littman D R. (Department of Microbiology and Immunology, University of California, San Francisco 94143-0414.) JOURNAL OF VIROLOGY, (1992 Jan) 66 (1) 524-33. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The third hypervariable (V3) domain of the human immunodeficiency virus type 1 (HIV-1) envelope glycoprotein has been proposed to play an important role in mediating viral entry. Antibodies to the V3 domain block HIV -1 infection but not virus binding to CD4. At the center of the V3 domain is a relatively conserved sequence of amino acids, GPGRA. It has previously been shown that mutation of some of these amino acids reduced the ability of gp160 expressed on the surface of cells to induce fusion with CD4-bearing cells. In order to analyze the role of V3 domain sequences in mediating HIV entry, we introduced several amino acid substitution mutations in the GPGRA sequence of gp160 derived from HIV-1 strain HXB2 and in the analogous sequence of strain SF33, GPGKV. Virus was generated by cotransfecting the env constructs and a selectable env -negative HIV vector, HIV-gpt. When complemented with a retrovirus env gene, infectious virus capable of a single round of replication was produced. The viral particles produced were analyzed biochemically for core and envelope proteins and for infectious titer. The transfected envs were also analyzed for ability to bind to CD4 and mediate cell fusion. Several of the amino acid substitutions resulted in moderate to severe decreases in virus infectivity and fusion activity. Envelope glycoprotein assembly onto particles and CD4 binding were not affected. These results provide evidence that V3 sequences are involved in mediating the fusion step of HIV-1 entry.

L17 ANSWER 167 OF 189 MEDLINE

92118456 Document Number: 92118456. PubMed ID: 1768461. Alteration of HIV-1 infectivity and neutralization by a single amino acid replacement in the V3 loop domain. Ivanoff L A; Looney D J; McDanal C; Morris J F; Wong-Staal F; Langlois A J; Petteway S R Jr; Matthews T J. (Department of Antiinfectives, SmithKline Beecham Pharmaceuticals, King of Prussia, PA 19406-0939.) AIDS RESEARCH AND HUMAN RETROVIRUSES, (1991 Jul) 7 (7) 595-603. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB The V3 loop (residues 303-338) of the human immunodeficiency virus type 1 (HIV-1) gp120 envelope protein represents a principal neutralizing determinant for the virus. An HIV-1 proviral clone containing a mutation in the V3 loop was constructed in which the proline residue at position 313 was changed to an alanine (P313-A). This mutation alters the conserved GPGR sequence that is found in the V3 loop sequences of different HIV-1 isolates. The P313-A clone produced virus particles, which were infectious for a number of T-cell lines including MOLT-4, CEM, and SupT1, but demonstrated a relatively low infectivity on the AA5 B-cell line when compared with wild-type viruses, HTLV-IIIB, HXB2/10 (a chimeric molecular clone), and another mutant virus (Q290-T). V3 loop-specific neutralizing polyclonal sera and the 9284 monoclonal antibody, which recognizes the amino side of the V3 loop sequence, effectively blocked infectivity and syncytia formation of all viruses tested. In contrast, the 0.5 beta monoclonal antibody, which is biologically more potent than 9284 and recognizes a different V3 loop determinant, failed to neutralize the P313-A virus. These results suggest that the proline residue in the relatively conserved GPGR "turn" region of the V3 loop is crucial for recognition by the 0.5 beta antibody. The observed variation in sensitivity of the B-cell line to the P313-A virus may reflect the presence of cell-specific factors which could be important in establishing an HIV-1 infection.

L17 ANSWER 66 OF 189 MEDLINE

1999400476 Document Number: 99400476. PubMed ID: 10471286. Effect of nonpolar substitutions of the conserved Phe11 in the fusion peptide of HIV-1 gp41 on its function, structure, and organization in membranes. Pritsker M; Rucker J; Hoffman T L; Doms R W; Shai Y. (Department of Biological Chemistry, Weizmann Institute of Science, Rehovot, Israel.) BIOCHEMISTRY, (1999 Aug 31) 38 (35) 11359-71. Journal code: 0370623. ISSN: 0006-2960. Pub. country: United States. Language: English.

AB The fusion domain of the HIV-1 envelope glycoprotein (gp120-gp41) is a conserved hydrophobic region located at the N-terminus of the transmembrane subunit (gp41). A prominent feature of this domain is a conserved five-residue "FLGFL" sequence at positions 8-12. Mutation of the highly conserved Phe(11) to Val (F11V), presumed not to significantly affect the hydrophobicity and the structure of this region, has been shown to decrease the level of syncytium formation and virus infectivity. Here we show that the substitution of Gly for Phe(11) (F11G) reduces cell-cell fusion activity by 80-90%. To determine the effect of these mutations on the properties of the fusion peptide, a 33-residue peptide (WT) identical to the extended fusion domain and its F11V and F11G mutants were synthesized, fluorescently labeled, and studied with respect to their function, structure, and organization in phospholipid membranes. The WT peptide alone induced fusion of both zwitterionic (PC/Chol) and negatively charged (PS/PC/Chol and POPG) vesicles, in contrast to a 23-mer fusion peptide lacking the C-terminal domain which has been shown to be inactive with PC vesicles but able to induce fusion of POPG vesicles which had been preaggragated with Ca(2+) or Mg(2+). The F11V peptide preserved 50% activity, and the F11G peptide was virtually inactive. ATR-FTIR spectroscopy indicated similar secondary structure of the peptides in multibilayers that was independent of membrane composition. Furthermore, all the peptides increased the extent of lipid disorder to a similar extent, but the kinetics of amide II H to D exchange was in the following order: F11G > F11V > WT. Fluorescence studies in the presence of membranes, as well as SDS-PAGE, revealed that the WT and F11V peptides self-associate to similar levels while F11G exhibited a decreased level of self-association. The data suggest that the FLGFL motif contributes to the functional organization of the HIV-1 fusion peptide and that the C-terminal domain following the fusion peptide contributes to the membrane fusion process.

L20 ANSWER 23 OF 26 MEDLINE
92219412 Document Number: 92219412. PubMed ID: 1560543. Phenotype-associated sequence variation in the third variable domain of the human immunodeficiency virus type 1 gp120 molecule. Fouchier R A; Groenink M; Kootstra N A; Tersmette M; Huisman H G; Miedema F; Schuitemaker H. (Department of Clinical Viro-Immunology, Central Laboratory of The Netherlands Red Cross Blood Transfusion Service, Amsterdam.) JOURNAL OF VIROLOGY, (1992 May) 66 (5) 3183-7. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The third variable (V3) domain has been implicated in determining the human immunodeficiency virus (HIV) phenotype, including fusion capacity and monocytotropism. In a large set of primary HIV type 1 (HIV-1) isolates, V3 sequence analysis revealed that fast-replicating, syncytium-inducing isolates contained V3 sequences with a significantly higher positive charge than those of slow-replicating, non-syncytium-inducing monocytotropic isolates. It appeared that these differences in charge could be attributed to highly

variable amino acid residues located on either side of the V3 loop, midway between the cysteine residues and the central GPG motif. In non-syncytium-inducing monocytotropic isolates, these residues were negatively charged or uncharged, whereas in syncytium-inducing nonmonocytotropic isolates, either one or both were positively charged. The substitutions at these positions result in changes in the predicted secondary structure of the V3 loop. Our data suggest that two amino acid residues in the highly variable V3 domain are responsible for phenotype differences and point to conformational differences in V3 loops from phenotypically distinct HIV-1 isolates.

L20 ANSWER 17 OF 26 MEDLINE
95363409 Document Number: 95363409. PubMed ID: 7636471. Impact of natural sequence variation in the V2 region of the envelope protein of human immunodeficiency virus type 1 on syncytium induction: a mutational analysis. Andeweg A C; Boers P H; Osterhaus A D; Bosch M L. (Laboratory of Immunobiology, National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands.) JOURNAL OF GENERAL VIROLOGY, (1995 Aug) 76 (Pt 8) 1901-7. Journal code: 0077340. ISSN: 0022-1317. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Several studies have demonstrated a functional role for the V1-V2 region of the human immunodeficiency virus type 1 (HIV-1) envelope surface glycoprotein gp120 in the membrane fusion processes underlying viral entry and syncytium induction. In a study with chimeric primary envelope genes, we have previously demonstrated that the exchange of V2 regions was sufficient to transfer syncytium-inducing capacity to a non-syncytium-inducing envelope protein. The exchanged V2 regions, comprising a number of variable amino acids, conferred changes to both the predicted secondary structure and to the net positive charge of the V2 loops. In a syncytium-forming assay based on transient envelope protein expression in CD4+ SupT1 cells, we have extended this observation by mutating the variable positions of the V2 region to determine the relative contribution of individual amino acids to syncytium formation. It can be shown that simultaneous mutation of multiple amino acids is needed to interfere with the V2 region-determined syncytium-inducing phenotype. **Single amino acid changes either influencing charge of predicted secondary structure of the V2 loop proved to be insufficient to abolish V2 region-controlled syncytium formation. This robust V2 organization may allow the virus to accumulate mutations, while retaining its biological phenotype.**